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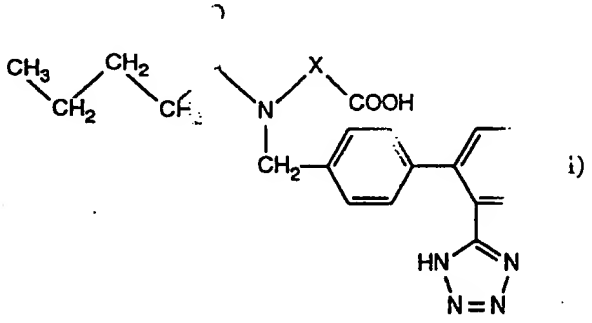
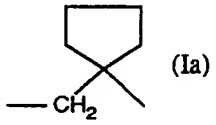
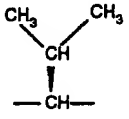
(54) Title: TREATMENT OF GLAUCOMA



i)



(Ia)



(Ib)

(57) Abstract

The present invention relates to the use of the compounds of formula (I), wherein X is (Ia), or X is (Ib), the carboxy group being linked directly to the cyclopentyl ring in the case where X = (Ia), and their salts in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal)intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy, and also to corresponding ophthalmic compositions.

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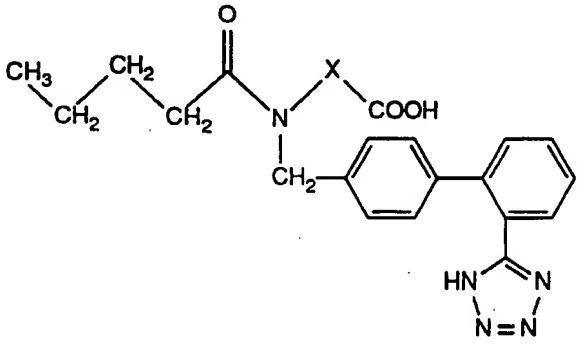
Treatment of glaucoma

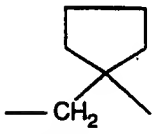
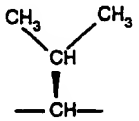
The term glaucoma covers pathological symptoms of the eye that are attributable to elevated intra-ocular pressure. Obstruction of the movement of aqueous humour often causes an increase in intra-ocular pressure. Chronically increased intra-ocular pressure has a damaging effect on the optic nerve and the retina, which can result not only in a restricted field of vision but also in blindness.

Accordingly, the search for active ingredients that are able significantly to reduce intra-ocular pressure is regarded as very important. U.S. Patent No. 5 036 048 describes angiotensin-II antagonists as being suitable agents for the treatment of glaucoma.

Extensive pharmacological studies have shown that the compounds of the formula



(I), wherein

X is  (Ia) or X is  (Ib), the carboxy group being linked directly to the cyclopentyl ring in the case where X = (Ia), and their salts are suitable to a surprising degree for reducing intra-ocular pressure. This effect is achieved not only by the topical administration of the active ingredient but also by its systemic administration.

The compounds of formula (I) and their salts were also found to have a surprisingly long duration of action when used in the treatment of male albino rats, in which intra-ocular

hypertension had been produced, using the glucocorticoid model.

The compounds of formula (I) or salts thereof are also distinguished by being extremely well tolerated by the eye, which can be demonstrated in a test model using rabbits' eyes. For that purpose, eye drops comprising the active ingredient in different concentrations are administered to the conjunctival sac of animals of the Himalaya type (pigmented), for example over a period of five days. Ophthalmological and ophthalmopathological examinations revealed no local or systemic intolerances.

Another surprising effect is that the compounds of formula (I) and their salts have a vaso-relaxing effect on the eye, both when administered topically and when administered systemically, and can accordingly be used in the treatment of vasospastic constitutions of the eye.

In addition, the compounds of formula (I) and their salts can be used in the treatment of diabetic retinopathy.

The compounds of formula (I) and their salts are described in the European Patent Application having the publication number 443 983 as angiotensin-II antagonists, in particular specifically in Examples 16 [(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine] and 40 [N-(2-carboxy-2,2-tetramethylene-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine].

The present invention relates to the use of the compounds of formula (I) and their salts in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, being the aqueous humour, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy.

The present Application relates also to a method of treating glaucoma, increasing the movement of (retinal) intra-ocular fluid, treating vasospastic constitutions of the eye and treating diabetic retinopathy, which method comprises administering to patients requiring such treatment a therapeutically effective amount of a compound of formula (I) or of a pharmaceutically acceptable salt thereof.

Compounds (I) and, where appropriate, their tautomers may be in the form of salts.

especially pharmaceutically acceptable salts. Because compounds (I) have, for example, at least one basic centre, they can form acid addition salts. The latter are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanecarboxylic acids, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanesulfonic or arylsulfonic acids, for example methane- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed with any additional basic centre that may be present. Furthermore, compounds (I), having the acidic 5-tetrazolyl group, can form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propyl-amine, or a mono-, di- or tri-hydroxy-lower alkylamine, for example mono-, di- or tri-ethanolamine. Corresponding internal salts can also be formed.

The present Application relates also to pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy, comprising a therapeutically effective amount of a compound of formula (I) or of a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable formulation agent suitable for ophthalmic and for systemic use.

Corresponding ophthalmic compositions are advantageously administered topically to the eye, especially in the form of a solution, an ointment, a gel or a solid insert. Such compositions comprise the active ingredient, for example, in a range of from approximately 0.01 to approximately 10.0 % by weight, preferably from approximately 0.5 to approximately 5.0 % by weight. Unit dose forms of the active ingredient comprise, for example, from approximately 0.001 to approximately 5.0 % by weight, especially from approximately 0.05 to approximately 2.0 % by weight, preferably from approximately 0.1 to approximately 1.5 % by weight, more especially from approximately 0.1 to approx-

imately 1.0 % by weight, of active ingredient. The dose of the active ingredient may depend on various factors, such as mode of administration, requirement, age and/or individual condition.

There are used for corresponding ophthalmic compositions customary pharmaceutically acceptable excipients or additives known to the person skilled in the art, for example those of the type mentioned below, especially with the addition of isotonising agents, buffers, complexing agents, solubilisers and thickeners. Examples of such excipients and additives can be found in the PCT Patent Application having the publication number WO 91/15206. Such compositions are prepared in a manner known per se, for example by mixing the active ingredient with the corresponding excipients and/or additives to form corresponding ophthalmic compositions. The active ingredient is preferably administered in the form of eye drops, being dissolved especially in a sterile, aqueous isotonic solution which, if necessary, is buffered to the desired pH value.

Accordingly, the invention relates likewise to systemically administrable pharmaceutical compositions that comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient, and to a process for the preparation thereof.

Those pharmaceutical compositions are for enteral, such as oral, and also rectal or parenteral administration to warm-blooded animals, the pharmacological active ingredient being comprised on its own or together with customary pharmaceutical excipients. The pharmaceutical compositions comprise, for example, approximately from 0.1 % to 100 %, preferably from approximately 1 % to approximately 60 %, of the active ingredient. Pharmaceutical compositions for enteral or parenteral and also for ocular administration are, for example, compositions in unit dose forms, such as dragées, tablets, capsules or suppositories, and also ampoules. Those compositions are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and, if desired, processing the mixture or granules, if necessary after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes

using, for example, corn, wheat, rice or potato starch, gelatin, gum tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical compositions include dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may likewise be added.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatin rectal capsules that comprise a combination of the active ingredient and a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

For parenteral administration there are suitable especially aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or

aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, also stabilisers.

The dose of the active ingredient may depend on various factors, such as the mode of administration, species of warm-blooded animal, age and/or individual condition.

The present Application relates also to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope thereof in any way.

Formulation Examples 1, 2 and 3: A solution, comprising 20 mg of active ingredient, for example (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine, can be made up as follows:

Composition:

1)

active ingredient	20.00	mg
NaOH.1N	86.00	mg
benzalkonium chloride	0.10	mg
disodium ethylenediamine tetraacetate	0.50	mg
sorbitol	10.00	mg
$Na_2HPO_2.2H_2O$	9.91	mg
K_2HPO_4	0.44	mg
water (purity: pro inj.) ad	1.00	ml

2)

active ingredient	20.00	mg
NaOH.1N	86.00	mg
Macrogol 400	20.00	mg
benzalkonium chloride	0.10	mg

disodium ethylenediamine tetraacetate	0.50	mg
sorbitol	6.00	mg
$Na_2HPO_2.2H_2O$	9.73	mg
K_2HPO_4	0.43	mg
water (purity: pro inj.) ad	1.00	ml

3)

active ingredient	20.00	mg
NaOH.1N	86.00	mg
Polyoxyl 35 castor oil	4.00	mg
benzalkonium chloride	0.10	mg
disodium ethylenediamine tetraacetate	0.50	mg
sorbitol	6.00	mg
$Na_2HPO_2.2H_2O$	9.91	mg
K_2HPO_4	0.44	mg
water (purity: pro inj.) ad	1.00	ml

For this purpose, the constituents are introduced into water and dissolved.

Formulation Examples 4 and 5 for eye drops:

Vehicle:

$Na_2HPO_4.12\ H_2O$	3.58 g
NaCl	0.29 g
H_2O	100 ml

Active ingredient:

N-(2-carboxy-2,2-tetramethylene-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

4) 5 % active ingredient solution:

vehicle	0.995	ml
NaOH 2N	0.015	ml
active ingredient (5 %)	50	ml

pH = 6.0

5) 0.5 % active ingredient solution:

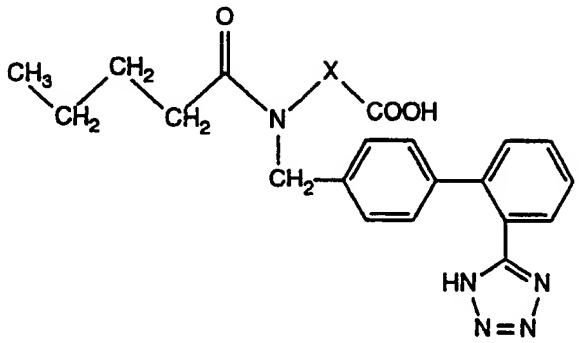
vehicle	0.9	ml
active ingredient (5 %)	0.1	ml

pH = 7.0

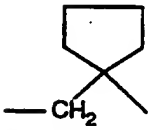
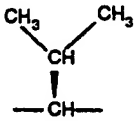
A compound of formula (I) or a pharmaceutically acceptable salt thereof can be processed in an analogous manner, for example as described in the above Examples.

What is claimed is:

1. The use of a compound of formula (I)



(I), wherein

X is  (Ia) or  (Ib), the carboxy group being linked directly to the cyclopentyl ring in the case where X = (Ia), or a pharmaceutically acceptable salt thereof in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy.

2. The use of the compound (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine or a pharmaceutically acceptable salt thereof in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy.

3. The use of the compound N-(2-carboxy-2,2-tetramethylene-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine or a pharmaceutically acceptable salt thereof in the preparation of pharmaceutical compositions for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy.

4. An ophthalmic composition for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy, comprising a therapeutically effective amount of

a compound of formula (I) according to claim 1 or of a pharmaceutically acceptable salt thereof.

5. A systemically administrable composition for the treatment of glaucoma, for increasing the movement of (retinal) intra-ocular fluid, for the treatment of vasospastic constitutions of the eye and for the treatment of diabetic retinopathy, comprising a therapeutically effective amount of a compound of formula (I) according to claim 1 or of a pharmaceutically acceptable salt thereof.

6. A method of treating hypertension, cardiac insufficiency and glaucoma, increasing the movement of (retinal) intra-ocular fluid, treating vasospastic constitutions of the eye and treating diabetic retinopathy, which method comprises administering to patients requiring such treatment a therapeutically effective amount of a compound of formula (I) according to claim 1 or of a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/01431

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/41

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 443 983 (CIBA-GEIGY AG) 28 August 1991 cited in the application see abstract see page 5, line 36 - line 43 see page 6, line 24 - line 29 see page 18, line 32 - line 37; claims; examples 16,40	4-6
Y		1-3
Y	US,A,5 036 048 (WATKINS) 30 July 1991 cited in the application see abstract see claims 1,12-14	1-3

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° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 MAY 1993	10.06.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HOFF P.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO,A,9 114 679 (SANOFI) 3 October 1991 see abstract see page 1, line 14 - line 25; examples 5,40-42	1-3
Y	THE FASEB JOURNAL vol. 5, no. 5, 1991, page A1218 S. WILSON ET AL. 'THE OCULAR HYPOTENSIVE EFFECT OF DUP 753, A NON-PEPTIDE ANGIOTENSIN II ANTAGONIST' see the whole document	1-3
Y	CARDIOVASCULAR DRUG REVIEWS vol. 9, no. 4, 1991, pages 317 - 339 P.C. WONG ET AL. 'LOSARTAN (DUP 753), AN ORALLY ACTIVE NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONIST' see the whole document, in particular page 333	1-3
P,Y	FR,A,2 672 891 (SYNTHELABO) 21 August 1992 see abstract see page 17, line 4 - line 13 see claims 1-5; examples 11,12,32	1-3

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9301431
SA 70804

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0443983	28-08-91	AU-A-	7115191	22-08-91
		JP-A-	4235149	24-08-92
US-A-5036048	30-07-91	US-A-	5182264	26-01-93
		ZA-A-	8701653	07-09-87
WO-A-9114679	03-10-91	FR-A-	2659967	27-09-91
		FR-A-	2665702	14-02-92
		AU-A-	7561091	21-10-91
		CA-A-	2057913	21-09-91
		EP-A-	0454511	30-10-91
		JP-T-	4506222	29-10-92
FR-A-2672891	21-08-92	None		